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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/554,314

04/19/2006

Christoph Hock

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EXAMINER

WANG, CHANG YU

ART UNIT

PAPER NUMBER

1649

MAIL DATE

DELIVERY MODE

05/28/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,314	HOCK ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 February 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-7 and 11-18 is/are pending in the application.
- 4a) Of the above claim(s) 11-17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3-7 and 18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>5/8/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed 2/25/08 is acknowledged. Claims 2 and 8-10 are cancelled. Claim 1 is amended. Claims 1, 3-7 and 11-18 are pending in this application. Claims 11-17 are withdrawn without traverse (the response filed on 6/1/07) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.
2. Claims 1, 3-7 and 18 are under examination in this office action.
3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.
4. Applicant's arguments filed on 2/25/08 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Maintained

5. The rejection of claims 1-4, 8 and 18 under 35 U.S.C. 102 (b) as being anticipated by Dodel et al. (EP1172378, published on Jan 16, 2002) is withdrawn in response Applicant's cancellation of claims 2 and 8, and Applicant's amendment to the claims by reciting "a tissue section".

The rejection of claims 1-10 and 18 under 35 U.S.C. 102 (e) as being anticipated by Schenk et al. (US Patent No. 6787523, published Sept 7, 2004, priority Dec 2, 1997) is withdrawn in response Applicant's cancellation of claims 2 and 8, and Applicant's

amendment to the claims by reciting "contacting a test sample with a tissue section containing b-amyloid plaques".

Claim Rejections/Objections Maintained

In view of the amendment filed on 2/25/08, the following rejections are maintained.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-7 and 18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting an increased level of immunostaining on brain sections of APP^{SW}xPS1^{M146L} double-transgenic mice or increased levels of antibodies against β -amyloid in serum and CSF samples of Alzheimer disease (AD) patients who are immunized with A β peptides, AN1792(QS-21), and detecting a positive correlation between the increased immunostaining and improvement of immunization treatment in AD patients, does not reasonably provide enablement for a method of monitoring an immunotherapy in a subject suffering from Alzheimer's disease by contacting all types of test samples with all forms of amyloid plaque (including all fragments, derivatives or mutants) in all types of tissue sections and comparing the level of immunoreactivity to an undefined reference value of AD as broadly claimed. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The rejection is maintained for the reasons made of record in the office action mailed 8/17/07, and as follows.

At p. 9 of the response, Applicant argues that the rejection has been overcome because independent claim 1 has been amended to recite specific disease and the specification is enabling for the amended claims. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, amended claim 1 still encompasses use of different test samples and use of different tissue sections that is not supported by specification or prior art. As previously made of record, the specification teaches that "the analyses of antibody titers measured by ELISA failed to predict the clinical outcome" (p.2) and also teaches "the TAPIR scores of the immune sera as determined by analyzing human β -amyloid on brain sections of transgenic mice were more predictive for the therapeutic outcome than antibody titers measured by ELISA" (p.7). Thus, only brain sections of APP^{SW}xPS1^{M146L} double-transgenic mice can be used in the claimed method. In addition, amended claim 1 recites "a reference value of immunotherapy representing AD", "a level of immunoreactivity prior to the onset of immunotherapy", and "a higher level of immunoreactivity as compared to the reference level of immunoreactivity...". However, the specification fails to provide a standard for ascertaining the requisite degree of the recited reference value or level, a skilled artisan would not know what to compare since the reference value or level is unknown.

Further, claim 7 recites brain sections from a transgenic mice for all forms APP including undefined fragments, derivatives or mutants. The specification fails to teach these undefined APP fragments, derivatives or mutants are and what other transgenic mice for these undefined fragments, derivatives or mutants are and can be used in the claimed method. Since other types of transgenic mice for undefined APP fragments or derivatives or mutants are unknown, it is unpredictable whether the brain sections derived from these undefined fragments or derivatives or mutants can be used in the claimed method. Thus, Applicant is not enabled the claimed method commensurate in scope with the claims without undue experimentation.

The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, it is unpredictable what transgenic mice for human APP fragments, derivatives or mutants are and can be used in the claimed method, and the experimentation left to those skilled in the art is extensive and undue. See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation.

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-7 and 18 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is maintained for the reasons made of record in the office action mailed 8/17/07, and as follows.

At p. 10 of the response, Applicant argues that amended claims are not indefinite because independent claim 1 has been amended to recite "a reference level of immunoreactivity representing AD" or "a level of immunoreactivity determined prior to onset of said immunotherapy in said subject". Applicant's arguments have been fully considered but they are not persuasive.

In contrast, the specification fails to teach what a reference value of immunoreactivity representing AD is and what a level of immunoreactivity determined prior to onset of said immunotherapy in the subject is. The specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Amended claim 1 also recites a "higher level of immunoreactivity as compared to the reference level of immunoreactivity...". Since the reference value or the level of immunoreactivity prior to immunotherapy is unknown, a skilled artisan would not know what value or level would be considered higher. The metes and bounds of the reference value or level cannot be determined, thus the claims are indefinite.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-7 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dodel et al. (EP1172378, published on Jan 16, 2002 as cited in the previous office action) in view of Schenk et al. (Nature. 1999. 400: 173-177). The rejection is maintained for the reasons made of record in the office action mailed 8/17/07, and as follows.

At p. 14-16 of the response, Applicant argues that applied references do not render the claimed method obvious because neither Dodel nor Schenk teaches contacting test samples with a tissue section containing β -amyloid plaques, determining the level of immunoreactivity of the test sample with β -amyloid plaques present in the

amyloid amyloid plaque-containing tissue section. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, the examiner asserts that the applied references do teach the claimed method. Dodel (EP'378) teaches detection of the levels of anti-A β antibodies and A β peptides in plasma and CSF as in claims 1, 3, 4 and 18 as compared to controls or before treatment (i.e. comparing the level of immunoreactivity between a test sample and an amyloid plaque-containing sample and reference value as in claims 1, 3-4, 8 and 18; see col.3 [0019]; col. 6 [0038]). Although Dodel does not teach contacting serum or CSF with a tissue or brain section containing amyloid-plaques or derived from non-human transgenic mice, Schenk teaches detecting the level of antibodies in serum and CSF after treatment or immunization with AN1792 by an ELISA using different brain regions, which contain Amyloid-plaques as recited in instant claims 1 and 5-7. Schenk also teaches a positive correlation of treatment with Abeta peptides or anti-Abeta antibody with the effect of amyloid plaque reduction by immunohistochemical staining on brain sections of transgenic PDAPP mice (see col.19, lines 3-4; col.19, lines 6-32; cols.22-28). The serum and CSF obtained from patients and animals immunized with A β peptides are the test sample as recited in instant claims 1 (test sample) and 4 (body fluid) and 18 (serum or CSF). The teachings of detection of a positive correlation Amyloid plaque reduction and the level of anti-Abeta by Schenk et al. indicate that anti-Abeta decreases Abeta burden on the brain by immunoreacting with Abeta and thereby depleting Abeta accumulation (amyloid plaques) on the brain. Thus, it is predicted and expected to detect an increased immunoreactivity on brain tissue sections of transgenic

animals contacted with test CSF or serum from patients or animals of immunotherapy because the anti-Aβ antibodies generated from patients or animal with immunotherapy of Aβ immunization are increased in serum and CSF and are derived from the same epitopes of Aβ (immunogen) as brain sections of transgenic animals (amyloid-plaque containing tissue sections). Thus, the increased immunoreactivity as compared to prior to immunotherapy on brain sections is expected.

Accordingly, the claimed method as recited in instant claims are obvious over the applied references because animals or patients immunized with Aβ generate anti-Aβ antibodies against Aβ plaques and show reduced Aβ burden or increased Aβ clearance, which is an increased level of immunoreactivity of antibodies against Aβ, as taught by Schenk et al.. Thus, one of ordinary skill in the art would have expected success in monitoring an immunotherapy in a subject suffering from AD by use of brain sections of transgenic animals containing amyloid plaques as a tool to detect the anti-Aβ level of immunization and to detect the immunoreactivity between immunogens (Aβ) and antibodies against the immunogens because animals or patients immunizing with Aβ generate anti-Aβ antibodies and show reduced Aβ burden, which is increased immunoreactivity and is as an indicator of improvement of the immunotherapy in AD.

Note that

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980); see also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992). See MPEP § 2144.06.

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"The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

At p.15 of the response, Applicant argues that the claimed invention is a better indicator of a positive clinical outcome in AD immunotherapy than the conventional ELISA method because high levels of immunoreactivity as determined by the claimed method show beneficial clinical effects as compared to the ELISA method. Applicant's arguments have been fully considered but they are not persuasive.

In response, both Dodel and Schenk teach methods of monitoring immunotherapy by detecting the level of anti-Abeta with an ELISA method including using brain homogenates. In addition, Schenk also teaches immunohistochemical analysis to monitor immunotherapy and correlates with the effect of anti-Abeta with the level of anti-Abeta. Both Dodel and Schenk's methods are effective and sufficient to monitor immunotherapy of Abeta immunization. Note that

"Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)" See MPEP § 2143. 01-I.

In addition,

"A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). See MPEP 716.02(a)-I.

Evidence of unexpected results must be weighed against evidence supporting *prima facie* obviousness in making a final determination of the obviousness of the claimed invention. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978). See MPEP 716.02(c)-I.

"Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967). See MPEP 716.02(c)-II.

Conclusion

9. NO CLAIM IS ALLOWED.

10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to

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6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/

Chang-Yu Wang, Ph.D.

May 22, 2008, 2008

/Christine J Saoud/

Primary Examiner, Art Unit 1647